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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,934	02/15/2002	Richard M. O'Hara JR.	GNN-028	3689

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BOSTON, MA 02109

EXAMINER
OUSPENSKI, ILIA I

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,934	O'HARA ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- Th MAILING DATE of this communication appears on the cover she t with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-12,14-20 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-12,14-20 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/28/02,8/4/03*. 6/27/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment/remarks, filed 06/27/2005, are acknowledged.

Claims 5, 13, and 21 have been cancelled.

Claims 1, 6 – 9, 14 – 16, and 22 – 24 have been amended.

Claims 25 – 27 have been added.

Claims 1 – 4, 6 – 12, 14 – 20, and 22 – 27 are pending.

2. This Office Action will be in response to applicant's arguments, filed 06/27/2005.

The rejections of record can be found in the previous Office Action, mailed 12/27/2004.

The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

3. Applicant's IDS, filed 06/27/2005, is acknowledged, and has been considered.

Further, references cited on IDS filed 10/28/2002, copies of which were submitted in response to the previous Office Action, have been considered.

4. The objections of record to the disclosure have been withdrawn in view of Applicant's amendment and arguments, except as set forth infra.

It is noted that in response to the objection of record to the disclosure of Example 4, which does not disclose the nature of treatment received by "control mice," Applicant argues that working examples are not required for an invention to be enabled, and that Applicant need not have actually reduced the invention to practice prior to filing.

With regard to "710-Fab," which is referenced in Figures 3 and 4 but not mentioned in the description, the objection of record is maintained for the reasons of record:

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the specification: "710-Fab." Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

5. Claims 1, 2, 6 – 10, 14 – 16, and 25 – 26 stand rejected under **35 U.S.C. 102(b)** as being anticipated by Linsley et al. (US Pat. 5,521,288, see entire document) as evidenced by Paul (Fundamental Immunology, 1999, page 451).

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that the instant claim language, as amended, excludes whole anti-CD28 antibodies from the scope of the claimed methods.

This is not found persuasive, because Linsley et al. teach that not only whole antibodies, but also fragments of anti-CD28 antibodies containing the antigen-binding portion can be used to downmodulate immune response (see entire document). In particular, Linsley et al. teach: "anti-CD28 antibodies may be screened to identify those capable of inhibiting the binding of the B7 antigen to CD28 antigen. The antibodies or antibody fragments such as Fab fragments may then be used to react with the T cells, for example, to inhibit CD28 positive T cell proliferation. The use of Fab fragments of the 9.3 monoclonal antibody, or Fab fragments of the anti-CD28Ig monoclonal antibodies as described herein, is expected to prevent binding of CD28 receptor on T cells to B7 antigen, for example on B cells. This will result in inhibition of the functional response of the T cells" (column 11 lines 53 – 63).

Applicant further argues that Linsley et al. fail to teach an isolated antigen binding portion of an anti-CD28 antibody that blocks signaling via CD28 in vivo, and thereby downmodulates an autoimmune response.

This is not found persuasive, because Linsley et al. teach: "the ligand for CD28, its fragments or derivatives, may be introduced in a suitable pharmaceutical carrier in vivo, i.e. administered into a human subject for treatment of pathological conditions such as immune system diseases or cancer. Introduction of the ligand in vivo is expected to result in interference with T cell/B cell interactions as a result of binding of the ligand to T cells. The prevention of normal T cell/B cell contact may result in decreased T cell activity, for example, decreased T cell proliferation" (column 12 lines 29 – 38). An anti-CD28 antibody is a ligand for CD28, as would be recognized by one of skill in the art, and also as taught by Linsley et al.: "It is expected that administration of the B7 antigen will result in effects similar to the use of anti-CD28 monoclonal antibodies reactive with the CD28 receptor in vivo" (column 10 lines 61 – 63). Linsley et

al. also teach that anti-CD28 antibodies downmodulate an autoimmune response, as evidenced by the following: "The inhibition of anti-CD28 and anti-B7 mAbs on the cognate T_h:B interaction also provide the basis for employing the CD28Ig and B7Ig fusion proteins, and monoclonal antibodies reactive with these proteins, to treat various autoimmune orders associated with exaggerated B cell activation such as insulin-dependent diabetes mellitus, myasthenia gravis, rheumatoid arthritis and systemic lupus erythematosus (SLE)" (column 36 lines 36 – 43).

Applicant further argues that later published work teaches that anti-CD28 Fab fragment does not block CD28 signaling in vivo in a mouse model for the autoimmune disorder, graft-versus-host disease (Yu et al., US Pat. Pub. No. 2002/0006403).

This is not found persuasive, because, contrary to Applicant's assertion, Yu et al. teach that "deaths of recipients treated with anti-CD28 Fab was delayed 4 – 5 days, as compared to those treated with control Abs" (paragraph 0247), i.e. treatment with anti-CD28 Fab fragment resulted in therapeutic downmodulation of an immune response.

Therefore, the rejection of record is maintained for the reasons of record, as it applies to the amended claims. The rejection or record is incorporated by reference herein, as if reiterated in full.

Newly added claims 25 and 26 are included in the rejection because, for example, Fab fragments of anti-CD28 antibodies taught by Linsley et al. are monovalent, as would be recognized by one skilled in the art, and as also evidenced e.g. by the instant specification at page 9, lines 15 – 16.

6. Claims 1 – 4, 6 – 12, 14 – 20, and 22 – 27 stand rejected under **35 U.S.C. 102(e)** as being anticipated by Yu et al. (US Pat. Pub. 2002/0006403, see entire document) as evidenced by Paul (Fundamental Immunology, 1999, page 451).

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that Yu et al. expressly contradict the instant claimed invention by providing evidence that an anti-CD28 Fab fragment is not effective in blocking CD28 costimulation (Example 4 at page 22, paragraphs 0246 and 0247).

This is not found persuasive, because, as noted supra and contrary to Applicant's assertion, Yu et al. teach that "deaths of recipients treated with anti-CD28 Fab was delayed 4 – 5 days, as compared to those treated with control Abs" (paragraph 0247), i.e. treatment with anti-CD28 Fab fragment resulted in therapeutic downmodulation of an immune response.

Therefore, the rejection of record is maintained for the reasons of record, as it applies to the amended claims. The rejection or record is incorporated by reference herein, as if reiterated in full.

Newly added claims 25 – 27 are included in the rejection because, as noted supra, Fab fragments of anti-CD28 antibodies taught by Linsley et al. are monovalent, as would be recognized by one skilled in the art, and as also evidenced e.g. by the instant specification at page 9, lines 15 – 16.

7. Conclusion: no claim is allowed.

8. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644

September 8, 2005

PHILLIP GAMBEL
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9/12/05